THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 49

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte ALEXANDER R. NEURATH, NATHAN STRICK,
YASMIN THANAVALA and MICHAEL PRIDE

_____

Appeal No. 1996-2539
Application 08/150,776[1]

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ON BRIEF

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Before WILLIAM F. SMITH, ROBINSON, and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

[1] Application for patent filed November 12, 1993.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 24 and 25, the only claims remaining in the application. The claims read as follows:

24. A vaccine comprising a hepatitis B virus surface antigen having the sequence (CTKPSDGNC) within residues S(139-147) and at least one non-permitted variant of said surface antigen where at least one of the following substitutions in S(139-147) is made:

at 141 K is substituted with D, E or R
at 142 P is substituted with S
at 143 T(S) is substituted with G, D, E, R, K or M
at 144 D is substituted with G, A, S, R, K, T or E
at 145 G is substituted with A, S, D, R or K; and
at 146 N is substituted with G, A, S, R, K or D

said vaccine being essentially free of permitted variants of hepatitis B virus surface antigen having the sequence (CTKPSDGNC) within residues S(139-147).

25. The vaccine of claim 24 wherein said at least one non-permitted variant of said surface antigen has at least one of the following substitutions in the S(139-147) sequence (CTKPSDGNC):

at 141 K is substituted with E
at 142 P is substituted with S
at 143 T(S) is substituted with M
at 144 D is substituted with N or E
at 145 G is substituted with A or R; and
at 146 N is substituted with D.

The references relied on by the examiner are:

Miyanohara et al. (Miyanohara)	4,778,761	Oct. 18, 1988

Hitzeman et al. (Hitzeman) 4,803,164 Feb. 7, 1989

Vyas 5,017,558 May 21, 1991

Brown et al. (Brown I), "Determination of the Affinity of Antibodies to Hepatitis B Surface Antigen in Human Sera," Journal of Immunological Methods, Vol. 72, pp. 41-48 (1984).

Brown et al. (Brown II), "Affinity of Antibody Responses in Man to Hepatitis B Vaccine Determined with Synthetic Peptides," The Lancet, July 28, 1984, pp. 184-187 (1984).

Okamoto et al. (Okamoto), "The Loss of Subtypic Determinants in Alleles *d/y* or *w/r*, on Hepatitis B Surface Antigen," Molecular Immunology, Vol. 26, No. 2, pp. 197-205 (1989).

Claims 24 and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate support in the specification as originally filed, i.e., as lacking an adequate written description. The claims also stand rejected under 35 U.S.C. § 103; as evidence of obviousness, the examiner relies on Miyanohara, Hitzeman, Brown I, Brown II, Vyas, Okamoto and "Applicants' Admission." We reverse both rejections.

DISCUSSION

Antibodies against Hepatitis B virus surface antigen (HBsAg), or S-protein, elicit protective immunity against HBV infection, and HBsAg is the immunogenic component of several hepatitis B vaccines. According to the specification, pages 3 through 7 (citations omitted):

> Several antigenic subtypes of HBV . . . have been recognized. All of these subtypes (for example ayw, adyw, adw2, adw and adr) share common (group specific) envelope epitopes, the immune response against which

> appears sufficient for protection against infection by any one of the virus subtypes.
>
> * * *
>
> [T]he S(139-147) segment of S-protein is part of an immunologically important region recognized by both B and T_h cells.
>
> Since the S(139-147) segment of the S-protein sequence is important for eliciting HBsAg-specific B and T_h-cell responses, amino acid replacements within this sequence may profoundly affect the recognition of the S-protein by both B- and T_h-cells and the specificity of immune responses to the S-protein. Among well-defined serological subtypes of HBsAg there is a single amino acid substitution (serine threonine) at residue 143. All other amino acid residues within this sequence are completely conserved among the distinct HBV subtypes.
>
> Evidence for the existence of genetic variants of HBV with envelope protein epitopes distinct from those present on already defined HBV subtypes has been reported recently.
>
> Amino acid replacements within the S-protein sequence may lead to a loss of subtype specific determinants d/y or w/r. [T]hese newly discerned HBV subtypes, which are nonreactive with subtype specific reagents developed earlier, still contain the group specific "a" determinants considered essential for eliciting protective immunity. However, HBV variants may have altered or insufficiently cross-reactive a determinants recognizable by antibodies and T cells elicited as a result of immunization with defined subtypes of HBV. Such variants may possibly cause infections not preventable by current hepatitis B vaccines. For this reason, it is important to define amino acid replacements within dominant group-specific B and T cell epitopes which would lead to the generation of escape mutants.

The claims are drawn to vaccines comprising HBsAg "having the sequence (CTKPSDGNC) within residues S(139-147)" and at least one HBsAg variant having at least one "non-permitted" amino acid substitution in the S(139-147) region, wherein the vaccines are "essentially free of permitted variants." According to the specification, non-

permitted amino acid substitutions are those that result in a variant having "less than 10% crossreactivity with the parent peptide at either the B cell or T cell level" (page 14).

Written Description

As set forth in Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), "the original disclosure of the application need only convey the concept now claimed in order for the written description requirement of 35 U.S.C. § 112, first paragraph, to be satisfied." The issue raised by the examiner is whether the original disclosure describes a vaccine "essentially free of permitted variants of hepatitis B virus surface antigen having the sequence (CTKPSDGNC) within residues S(139-147)."

The examiner notes that "the specification fails to explicitly teach the omission of permitted variants from the vaccines of the invention" and concludes that "[t]his silence cannot be construed as supporting a positive recitation of exclusion of permitted variants." Examiners Answer, Section (11). We disagree with the examiner's conclusion.

The specification discloses both permitted and non-permitted variants of HBsAg, and vaccine compositions comprising HBsAg and the non-permitted variants are expressly described. There is no mention of including permitted variants in the vaccines. On balance, we believe this speaks more towards not including permitted variants in the compositions, but it is true that the specification does not expressly exclude them. Thus, the specification conceivably conveys two concepts: (1) a vaccine composition including HBsAg, non-permitted variants and permitted variants, and (2) an otherwise identical

composition lacking the permitted variants. Appellants are free to define (and claim) their invention as one or the other, or both.

We find that the specification reasonably conveys the concept of a vaccine composition free of permitted HBsAg variants to one of ordinary skill in the art, and thus satisfies the written description requirement of 35 U.S.C. § 112, first paragraph. Accordingly, the rejection of claims 24 and 25 is reversed.[2]

Obviousness

As stated in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ 1626, 1629, (Fed. Cir. 1996) (citation omitted):

> It is well established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references.

Miyanohara, Hitzeman, Brown I, Brown II, and Vyas establish that vaccines comprising recombinant HBsAg were conventional at the time of the invention, and that the region of HBsAg including amino acids 139 to 147 was known to be a dominant epitope on the "a" group antigen of HBV. Moreover, Brown II states that the "a" group determinant "is present on all subtype variants of hepatitis B virus, and antibody to this group antigen confers protection against all subtypes" (Brown II, page 186, left-hand column).

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[2] 37 CFR § 1.75(d)(1) requires that "the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of terms in the claims may be ascertainable by reference to the description." We note that appellants have not complied with this rule.

The examiner relies on "Applicants' admission of the disclosure of McMahon" (at page 30 of the specification, and Table II) and Okamoto to "establish the sequences of rare subtypes having the sequences of the claimed non-permitted antigens" and concludes that:

> [I]t would have been prima facie obvious to a person having ordinary skill in this art to include synthetic peptides having the sequences of the rare subtypes disclosed by [Okamoto and McMahon] in a hepatitis vaccine thus achieving the invention as a whole. One would have been so motivated in view of the teachings of [Brown I or II] and Vyas that the 139-147 region is the location of important protective epitopes. (Examiner's Answer, Section (9)).

The examiner's rejection presupposes that one of ordinary skill in the art would have expected that conventional HBV vaccines would fail to protect against the rare subtypes reported by Okamoto and McMahon. Taking a step back, we find no basis in the art for this supposition.

Okamoto teaches that various amino acid substitutions (including substitutions at amino acid positions 144 and 145 of HBsAg) result in the loss of the HBV subtypic "d" determinant. While Okamoto speculates that HBsAg of deficient subtype would be difficult to identify in the presence of HBsAg of regular subtype, there is nothing in the reference to suggest that immunization with conventional HBV vaccines containing HBsAg would fail to protect against HBV of deficient subtype (page 203). In other words, there is nothing in Okamoto to suggest that any of the disclosed amino acid substitutions are "non-permitted" as that term is defined in the present specification, or that any of the disclosed variants

would lack the group specific "a" determinant recognizable by antibodies or T-cells elicited by immunization with conventional HBV vaccines containing HBsAg.

As for "Applicants' admission of the disclosure of McMahon," Table II of the present specification lists seven of the approximately forty "permitted" and "non-permitted" amino acid substitutions investigated by appellants (see also Figure 1). Some of the substitutions are attributed to the work of McMahon (unpublished at the time of filing) in identifying rare serological subtypes of HBV. Again, there is nothing, other than appellants' disclosure, to suggest that conventional vaccines containing HBsAg would be ineffective against HBV exhibiting any of the amino acid substitutions listed in Table II.

We have no doubt that the prior art could be modified in a manner consistent with appellants' specification and claims, but the fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Absent a recognition that conventional HBV vaccines would be ineffective against "non-permitted" variants, we find no reason stemming from the prior art which would have led a person having ordinary skill to the claimed method. In our judgment, the only reason or suggestion to combine the references in the manner proposed by the examiner comes from appellants' specification. The rejection of the claims under 35 U.S.C. § 103 is reversed.

REVERSED

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WILLIAM F. SMITH	)
Administrative Patent Judge	)
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	)
	) BOARD OF PATENT
DOUGLAS ROBINSON	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
TONI R. SCHEINER)	
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